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REACTIONS OF FLUOROALKYL-B-KETOESTERS WITH AMMONIA

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Esters of acetoacetic (AAE) and trifluoroacetoacetic (TFAAE) acids react with ammonia to give esters of β -aminocrotonic [1] and trifluoro- β -aminocrotonic [2] acids, respectively. Trifluoroacetoacetic esters reacts similarly with pentylamine in boiling benzene, but in CCl₄ or in the absence of solvent at ~ 20 °C the pentylammonium salt of TFAAE is obtained, which on heating loses H₂O to give the same product as in benzene [3]. In order to establish the effects of the structure of the fluoroalkyl substituent, the solvent (benzene, ether, or methanol), and the conditions on the course of the reaction, we have examined the reactions of the fluorinated β -ketoesters (Ia-f) with ammonia (Scheme 1).

Scheme 1

$$\mathbf{R} \underbrace{\mathbf{NH}_2}_{\mathbf{NH}_2 \mathbf{O}} \mathbf{H}_2 + \underbrace{\mathbf{RCONH}_2 + \mathbf{CH}_3\mathbf{CONH}_2}_{\mathbf{H}_2 \mathbf{O}}$$



(IV b,e), 29-42%

 $R = HCF_2(a), CF_3(b), H(CF_2)_2(c), C_3F_7(d), H(CF_2)_4(e), C_4H_9(f).$

With ammonia in the absence of a solvent at 100°C and on boiling in benzene, ether, or methanol compounds (Ia-f), irrespective of the length of the fluoroalkyl substituent, give the fluoroalkylated β -aminocrotonate esters (IIa-f), the structures of which were confirmed by their IR and PMR spectra (Table 1).

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n and a subscription of the subscription of th				Found	d/calc	ulated	.pct.		IR spe	ctrum,	V,	PMR s	Dectru	л, б.	TMS, CDC1 ₃ ,
Compound		Yield, pct.	mp (solvent)	C	н	Бч.	z	Empirical formula	<u>c=0</u>	c=c	HN	MeO	CH	HN	$_{\rm JHCF_2}^{\rm H(CF_2)n}$; $_{\rm HCF_2}^{\rm H(CF_2)n}$; $_{\rm HZ}^{\rm HZ}$
HCF, OMe															
NH ₃ 0	(II a, *	73	44-45 (hexane)	39,61 39,74	4,50	<u>24,73</u> 25,14	9,27 9,26	C ₅ H ₇ F ₂ NO ₂	1720	1650	$\begin{array}{c} 1695 \\ 3365 \\ 3510 \\ 3510 \end{array}$	3,70	4,84	6,30	6,0 t , 55,2
CF3 NH2 O	* (dII)	70	50-52 (hexane)	35,23 35,51	3,44 3,58	32,85 33,70	8,10 8,28	C5H6F3NO2	1720	1645	1690 3340 3510	3,78	4,85	6,20	
H(GFt)2 OMe	(IIC) *	87	97—98/3 mm	36,31 35,83	3,85 3,51	<u>37,68</u> 37,87	7,02 6,97	C ₆ H ₇ F ₄ NO ₂	1720	1646	1690 3350 3510	3,76	4,82	6,30	5,85 t.t , 54,2, 5,5
CsF7 OMe	(IIG) *	52	142-144 (hexane)	30,98 31,24	2,12 2,25	48,71 49,42	5,04 5,21	C7H6F7NO2	1710	1640	1690 3345 3515	3,67	4,71	6,40	
H(GF2)4 OMe	(IIe) *	46	62-64 (chloroform)	31,57 31,91	2,43	49,90 50,47	4,49 4,65	$C_8H_7F_8NO_2$	1710	1640	1690 3305 3500	3,60	4,98	7,10	6,48 t.t.
C.F. OMe	(II £) *	917	118-120 (hexane)	30,25	1.78	53,04 53,78	3,90 4,39	C ₈ H ₆ F ₉ NO ₂	1705	1640	$ \begin{array}{c} 1660 \\ 3200 \\ 3310 \\ 3310 \end{array} $	3,70	5,20	7,15	
CFF3 0-0-0 NH4	(111)	79	62-64 (decomp.)	32,46 32,09	4,10	30,26 30,46	7,87 7,49	C ₅ H ₈ F ₃ NO ₃	1670	1630	1570 2500	3,45	4,65	4,12	
CF ₃ NH ₃	(qAI)	. 53	4648	30,59	3,18	37,01	8,99	C,H4F3NO2	1670	1610	3340	₩ 6 ×12,	5,19	6,70	
H(CF,), NH,	(i V e)	42	(nexane) 73-75 (chloroform)	30,98 28,75 29,28	2,61 2,04 1,76	36,75 52,40 52,94	9,03 5,14 4,88	C7H5F8NO2	1660	1600	3210 3490		5,74	7,30	6,6 t.t.
CFI NHI	(d V)	, rÙ	69-71 (hexane)	<u>31,32</u> 30,97	3,36 3,89	35,90 36,74	18,00 18,06	C,HsFsNrO	1660	1600	1540 3180 3480 3480 3500 3500		5,05	0,0 15,0	
H(CF_A)	(V B)	12	47-48 (hexane)	29,00 29,38	2,03	53,00 53,11	9.70 9,79	$C_7 H_6 F_8 N_2 O$	1655	1610	1570 3160 3320 3460		4,95	5,54 6,55	6,02 t.t 52,7, 6,1
*The yields	of (IIa	-f) gi	lven are for	the	folle	swing	cond	itions:	100°C	- u	solv	ent,	open	syst	em.

TABLE 1. Products of the Reaction of Fluorinated 8-Ketoesters (Ia-f) with Ammonia

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The reaction of (Ib) with ammonia in ether at -20°C, or with aqueous ammonia at -5°C, gives the ammonium salt (III), which is stable at $\sim 20^{\circ}$ C (Table 1). such behavior is untypical of fluorine-free AAE and is apparently due to the high acidity of fluorinated β -ketoesters (Table 2) as compared with AAE (pK_a = 12.6 [7]). Heating the salt (III) in an ampul (6 h at 100°C) results in the elimination of water and the formation of (IIb).

Treatment of (Ia) with a threefold excess of ammonia in ether at 100°C in an autoclave gives 43% of (IIa), whereas (Ib) and (Ie) under the same conditions give the amides of the β -ketoacids (IVb, e) (Table 1). The absence from the PMR spectra of signals for the methylene group shows that these amides exist completely in the enol form.

Increasing the excess of ammonia to ten times under the conditions described above leads to the formation from (Ib, e) of the β -aminocrotonamides (Vb, e) (Table 1), fluorocarboxamides, and acetamide, whereas AAE and (Ia) give β -aminocrotonate ester (89%) and (IIa) (75%), respectively.

It may therefore be concluded that acetoacetic and 4,4-difluoroacetoacetic esters give with ammonia, irrespective of the reaction conditions, β -aminocrotonate and 4,4-difluoroaminocrotonate (IIa) esters, β -Ketoesters containing highly fluorinated substituents [CF₃ or H(CF₂)₄] also react with ammonia to give β -aminocrotonate esters (II), but under severe conditions β -aminocrotonamides (IVb, e) are formed. The latter react with a tenfold excess of ammonia in an autoclave to give β -aminocrotonamides (IVb, e) together with acetamide and fluorocarboxamides.

In order to establish the structures of (IIa-f), their PMR spectra and dipole moments (DMs) were measured. On cooling to -10° C, the signal for NH₂ in (IIa-f) was resolved into two one-proton signals, which on further cooling (-60° C) underwent a shift, one to lower field (7.50-7.60 ppm), and the other to higher field (4.90-5.20 ppm). The absence of splitting of the signals for =CH and MeO under these conditions is evidence of restricted rotation around the C-N bond. To calculate the barrier to this process, the $\Delta G\#$ values were calculated as described in [4] (Table 2) and were found to be \sim 50 kJ/mole with an error of 10-12% due to the presence of the quadrupole moment of the ¹⁴N nucleus, resulting in broadening of the H₂N signals. Somewhat greater values ($\Delta G\#$ = 55-59 kJ/mole) were found for fluorinated β -aminovinyl ketones with an amino group in the α position to the fluoroalkyl substituent [5].



The fairly low values of the experimental DMs for (IIa-f) (Table 2) are in the best agreement with the theoretical values (Scheme 2), calculated by the vector additive method, taking into account the DM of the fluoroalkyl group [6], the rotation of the amino group around the C-N bond, and a small additional DM (μ_{int}) arising from interaction of the NH₂ and CO groups through the π -system (polar conjugation) and intramolecular hydrogen bonding.

TABLE 2. Dipole Moments and $\Delta G \#$ Values for Rotation of the Amino Group and Ionization Constants pK_a for Fluoroalkylated β -Aminocrotonate Esters (IIa-e)

Compound	$R_{\mathbf{F}}$	^µ ехр	µtheo cis-s cis D	^r µ _{int}	pK _a	∆G#, kJ/mole	∑ _c ,°K
(II2) * (IIb) (IIc) (IId) † (IIe) +	$\begin{array}{c} \mathrm{HCF}_{2}\\ \mathrm{CF}_{3}\\ \mathrm{H}(\mathrm{CF}_{2})_{2}\\ \mathrm{C}_{3}\mathrm{F}_{7}\\ \mathrm{H}(\mathrm{CF}_{2})_{4} \end{array}$	$\begin{array}{c} 1,68\pm0,01\\ 1,62\pm0,01\\ 1,94\pm0,01\\ 2,42\pm0,01\\ 2,62\pm0,01\end{array}$	2,36 2,78 2,76 3,00	1,15 1,06 0,90 0,40	$7,9\pm0,1$ 6,97 $\pm0,02$ 6,02 $\pm0,07$ 5,94 $\pm0,03$	$50,85\pm5,49$ $50,80\pm5,16$ $50,91\pm5,65$	273 273 273

*Compound (IIa) was unstable under the conditions used to measure its pK_a value.

+Compounds (IId-f) were sparingly soluble in octafluorotoluene, in which the spectra were obtained, and (IIf) also under the conditions used in measuring μ_{exp} .

In the case of the cis-s-cis structure (Scheme 2). μ_{int} decreases the overall DM, the values calculated for (IIa-f) lying between 0.4 and 1.15 D (Table 2). These values are somewhat lower than those for the corresponding β -aminovinyl ketones (0.8-1.38 D), in agreement with the higher $\Delta G\#$ values of the latter.

The theoretical DMs calculated for all the trans and s-trans structures (2.9-5.2), Scheme 2) are higher than the experimental values, and their μ_{int} values must be oriented in such a way as to increase the overall DM. It may therefore be concluded that the DMs of (IIa-f) confirm that they exist as the cis-s-cis structures with hindered rotation of the amino group.

EXPERIMENTAL

The β -ketoesters (Ia-f) were obtained as described in [10]. The PMR spectra were obtained on Tesla BS-567 (100 MHz) and Perkin-Elmer R-12B (60 MHz) instruments, using TMS as the internal standard; and the IR spectra were obtained on a UR-20 spectrometer. The experimental DMs for (IIa-e) (Table 2) were calculated using the formula of Guggenheim and Smit [8], from the dielectric constants and refractive indices of benzene solutions of (IIa-e) over the concentration range 0.1-1.0 mole/liter at 25°C. The theoretical DMs of (IIa-f) (Table 2 and Scheme 2) were calculated by the additive vector from the values of the group dipole moments [6, 9]. The direction of the dipole moment μ_{int} (IIa-f) was assumed to be from nitrogen to the oxygen of the carboxy group.

The ionization constants of (IIa-f) (Table 2) were determined spectrophotometrically at 20°C on a Specord UV-VIS spectrophotometer. The pH values were measured on a pH-340 potentiometer with glass and silver electrodes. The concentration of the compounds was $8\cdot10^{-5}$ mole/liter in aqueous NaOH containing 5% of alcohol.

<u>Reaction of (Ia-f) with Ammonia in the Absence of Solvent</u>. Ammonia (50 mmoles) was bubbled into 30 mmoles of (Ia-f) at 35-40°C, and the mixture was then heated to 100°C for 1-2 h, and cooled. The solid which separated was recrystallized from hexane or chloroform [in the case of (IIc), it was distilled in vacuo] to give (IIa-f) (Table 1).

<u>Reaction of (Ib, e) with Ammonia in Ether, Benzene, or Methanol</u>. Ammonia was bubbled into a solution of 30 mmoles of (Ia, b, e) in 50 ml of solvent until the exothermic reaction ceased. The mixture was then boiled for 2-4 h, the solvent was distilled off, and the residue was recrystallized from hexane (IIa, b) or chloroform (IIe) (Table 1).

Reaction of (Ia, b, e) with Ammonia under Pressure. a) An autoclave was charged with a solution of 50 mmoles of (Ia, b, e) in 50 ml of dry ether, 150-180 mmoles of ammonia was added, and the mixture was heated for 8-10 h at 100°C. The ether was distilled off, and the residue was recrystallized from a suitable solvent to give (IIa) and (IVb, e) (Table 1).

b) The reaction was carried out similarly with 0.5 mmole of ammonia. After heating for 8-10 h, the mixture was cooled, and the ether and volatile products (ammonia and methanol) were distilled off. The resulting solid was extracted with ether (5×30 ml) to give the β -aminocrotonamides (Vb, e) (Table 1). The residue, consisting of fluorocarboxamides and acetamide, was identified with authentic samples by the IR spectra.

Ammonium Methyltrifluoroacetoacetate (III). a) Ammonia (50 mmoles) was passed into a solution of 6 g (33 mmoles) of (Ib) in 25 ml of dry ether at -20°C. The mixture was stirred 'for 0.3 h at -20°C, 30 ml of light petroleum cooled to 20°C was added, and the solid was filtered off to give 4.8 g (76%) of the salt (III) (Table 1).

b) To a mixture of 10 ml of 25% aqueous ammonia and 7 g of ice was added dropwise with stirring and cooling (-5°C) 15 g (90 mmoles) of (Ib), and the mixture was stirred for 2 h at -5°C. The solid was filtered off, washed twice with light petroleum cooled to 0°C (50 ml), and dried in a desiccator over NaOH to give 13 g (79%) of (III) (Table 1).

Methyl 4,4,4-Trifluoro-3-aminocrotonate (IIb). Into a 150-ml glass ampul was placed 4 g (21 mmoles) of the salt (III). The ampul was sealed, with the lower portion being heated for 6 h in a boiling water bath and the upper portion being cooled. The ampul was then opened, and the crystals that formed in the upper portion were recrystallized from hexane, yield 3.5 g (96%).

<u>β-Aminocrotonic Ester</u>. Into a steel autoclave was placed a solution of 8 g (66 mmoles) of ethyl acetoacetate in 50 ml of dry ether. Ammonia (\sim 60 mmoles) was added, and the mixture was heated to 100°C for 10 h. The autoclave was cooled then opened, and the ether was distilled off. The residue was distilled in vacuo to give 7 g (89%) of product bp 96-98°C (10 mm). Found: C 56.18; H 8.26; N 10.90%. C₆H₁₁NO₂. Calculated: C 55.80; H 8.58; N 10.85%. IR spectrum (ν , cm⁻¹): 1680 (C=O), 1610 (C=C), 1540, 3300, 3420 (NH₂). PMR spectrum (δ , ppm): 1.24 t, 4.08 q (5H, OC₂H₅), 1.31 (3H, CH₃), 4.49 (1H, -CH=), 7.32 (2H, NH₂).

CONCLUSIONS

1. It has been found that β -ketoesters containing highly fluorinated substituents [CF₃, or H(CF₂)₄] react with ammonia to give β -aminocrotonate esters, or under severe conditions, β -ketoamides. The latter react with a tenfold excess of ammonia to give β -aminocrotonamides together with acetamide and fluorocarboxamides.

2. Acetoacetic and 4,4-difluoroacetoacetic esters react with ammonia, irrespective of the reaction conditions, to give β -aminocrotonate and 4,4-difluoro- β -aminocrotonate esters.

3. Using DNMR and dipole moments, it has been shown that rotation of the amino group around the C-N bond in fluorinated β -aminocrotonate esters is restricted ($\Delta G \# \sqrt{50} \text{ kJ/mole}$).

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